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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/270,006	03/16/99	ROBIN J	017753-113

021839 HM22/0825
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EXAMINER	
BALASUBRAMANIAN, V	
ART UNIT	**PAPER NUMBER**
1624	9
DATE MAILED:	08/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/270,006	Robin et al.
Examiner	**Group Art Unit**
Venkataraman Balasubramanian	1624

☒ Responsive to communication(s) filed on *Jun 13, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-87* is/are pending in the applicat

Of the above, claim(s) *1-58 and 72-87* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *59-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants' response filed on 6/13/2000 is made of record. Applicant's election of group VI, claims 59-71 with traverse is acknowledged. Claims 1-58 and 72-87 are withdrawn from further consideration.

Applicants' traversal to restriction requirement, urging to joining groups I and IV-VI and VIII, is carefully considered but is found to be not persuasive for reasons of record. Following reasons also apply.

1. As noted by the applicants, group I pertains to process of making Ω-CO-O-CTX while groups IV-VI and VIII relates to chiral intermediates. Applicants agree these intermediates are new. Contrary applicants urging that they are structurally related, they are distinct having a varying core based on Z such as aza, oxa and thia ring compounds with varying ring size and open chain compounds. The method of making them are also different and each of them can be used for making products other than Ω-CO-O-CTX as well.
2. Furthermore, some compounds of these groups may be known in the prior art and it is believed that applicants would not acquiesce tb the rejection of non elected group IV, V and VII over prior art pertinent to compounds of group VI embraced herein. Note prior art R and R_1 below are relevant to Group VI.

Hence the restriction is proper and is maintained. The restriction is made **FINAL.**

Claims 59-71 are now pending.

Claim Rejections - 35 USC § 112

Claims 59-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. Claim 59 is indefinite as it recites "tertiary" heterocycloalkanes but all compounds embraced herein are not tertiary. Note when R^5, R^6 and R^8 are hydrogens, compounds embraced herein are not tertiary.

2. Recitation of Z as nitrogen is indefinite as the valence of nitrogen, as recited, is not met with and hence the structural make-up of the compounds embraced herein are indeterminate.

3. Claim 59 is indefinite as it recites "optionally including heteroatoms". It is not clear what heteroatoms are intended and how many hetero atoms are intended in the hydrocarbon radical. Hence the structural make-up of the hydrocarbon radical "optionally including heteroatoms" is indeterminate.

4. Recitation of n =0 in proviso 1 and 2 is improper and outside the scope of claim 59 as n is limited to values from 1 to 8 and not zero at all.

5. Again in claim 59, the recitation of functional groups such as carboxymethyl , O-methyl, OH etc. in the proviso 1-6 , have no antecedent basis as there is no recitation of these as substituents on the hydrocarbon radical in the definition of R^5, R^6 and R^8 . This clearly outside the scope of claim 59. Furthermore, the phrase " R^5 is not hydrogen; except for

compounds....." is confusing as it is not clear whether it is part of the following proviso or not. Note the semicolon after hydrogen.

6. Claim 60 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 60 which is dependent on claim 59 recites n = o which is outside the scope of claim 59 on which it depends.

7. Claim 61 and 63 are improper claim as it depends on claim 54 which belongs to the non-elected subject matter.

8. Claim 62 is an improper claim as it does not recite the definition of R^6, R^8 and n values.

9. Claim 66 which is an independent claim, is an improper claim as it does not recite the definition of R^5.

10. Claims 64, 65, 69 and 70 recite several "harringtonic acid" which is indefinite as the formula shown in those claim is not "harringtonic acid". Note compounds bearing CTX are outside the scope of claims 59-71.

11 Claims 59-71 have one or more typographical errors. See "oxacycloalcane", "racemix", "tertiary6 oxacycloalcane", "its ure", "eachone" etc.

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

> and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 59 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds where Z= O, does not reasonably provide enablement for compounds where Z=S . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specification provides no sufficient enabling disclosure by way of representative examples or reasonable disclosure of ultimate starting material sources for compounds where Z= S and N the plethora of groups permitted at instant R^5-R^8 variables which include substituted aryl ring , heterocycle ring, alkyl heterocyclealkyl (both with unspecified point of attachment). All examples shown are limited to compounds where Z= O. Synthesis of all complex molecules embraced in the invention therefore has to be enabled as commercial availability appears to be limited to only simple starting materials. See Ex parte Moersch, 104 USPQ 122; In re Howarth, 210 USPQ 689; In re Lund 153 USPQ 625; In re Wiggins, 179 USPQ 421.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Wasserman et al. US 4,178,286 or Ondetti et al. US 4,154,840.

Wasserman et al. teach several azacycloalkane carboxylic acids claimed herein. See formula shown on col. 2 and note the definition of R^1 and R^2 and n. Note n can 1-10. See the process of making shown on col. 3, line 40-60. See also examples 1-9 shown on col. 13-19. Although, applicants have not indicated what is the group on the nitrogen that meets the valence requirement (112/2, reason # 2) it is assumed that applicants are permitting substituents on the nitrogen. Furthermore, applicants should check Aldrich Catalog which sells some of the aza, thia and oxacycloalkane carboxylic acid compounds claimed herein (eg. proline, azetidine carboxylic acid and pipecolic acid). As for Ondentti et al. see formula III on col. 3 and example 1 on col. 10.

Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Henning et al. US 4,849,524.

Henning et al. teach process for preparing several proline derivatives claimed herein. See formula I on col. 2 and note the various R groups in the proline ring. See col. 1 through col. 4 for the process of making these compounds and examples 1-4 on col. 6-7 for compounds made.

Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Fritz-Langhals US 5,334,730.

Fritz-Langhals teaches a process for preparation of optically active carboxylic acids which include compounds claimed herein. See formula II on col. 2 and note when n= 1 or 2 and X = S or O, the compounds taught by the reference are also embraced herein. See col. 3 line 42-68 and col. 4, line 1-18 for making these compounds. Particularly note the references cited therein which assert the compounds are known in prior art. Furthermore, see examples 1- to 17 on col. 8-19 where Fritz-Langhals teaches use of these acids. As the specific species shown in examples use these acids , it is held that Fritz-Langhals had inherently made those compounds of formula III to get the final products shown in the examples. Note In re Petering et al 133 USPQ 275; In Re Schaumann, 195 USPQ 5.

Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Bosies et al.US 4,409,236.

Bosies et al teach several N-substituted aziridine-2-carboxylic acid derivatives which include compounds claimed herein. See general formula shown on col. 1 line 52 and note the definition of R, R_1 and X group. Note when X= COOH, the reference teaches compounds claimed herein. See col. 5-8 for the process of preparing these compounds . Especially see examples 9, 14 and 15.

Claim 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Newman et al. Organic Reactions, Volume V, page 414-440, 1952 or Levy et al US 2,889,339, US 2,889,340 or Kogure et al. US 4,042,617.

Newman et al. provides a review of Darzens glycidic ester condensation which includes compounds claimed herein. See the entire document , especially page 427-429 and Table I and II on

page 430-439. Similarly Levy et al. as well as Kogrue et al. teach several gylcidic acids claimed herein. The following references which are cumulative references are also provided to assist applicants to amend their claims: Nagoya et al. et al.US 3,725,437 ; Koyama et al. US 3,855,245 ; Kurono et al. 4,131,747; Bousquet et al. 5,081,240 ; Duchesne et al. 5,256,803.

Claim 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Eisetter et al. US 4,430,339.

Eisetter et al. teach several substituted oxirane carboxylic acids, which include compounds claimed herein, for use as medicaments including for treating disturbance of glucose and fat metabolism. See formula I on col. 1 and note the definition of various variables. Particularly see col.2 line 45-67, col. 3 through 4 for various oxirane carboxylic acid disclosed. See col. 7 through col. 10 for the process of making these compounds and examples 1-17 for compounds made shown on col.11-20.

Claim 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Mohrbacher et al. US 4,132,720.

Mohrbacher et al. teach several alkenyl substituted oxirane carboxylic acids, which include compounds claimed herein, for use as hypoglycemic agents. See formula I on col. 1 and note the definition of various variables. Particularly see col.2 through col. 4 for various oxirane carboxylic acid s and the process of making them. See col. 4 through col. 8 examples 1-XV for compounds made..

. Claim 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Delay US 4,252,728.

Delay teaches several norborane substituted oxirane carboxylic acids, which include compounds claimed herein, for use as perfumes .See formula I on col. 1 and note the definition of R. Particularly see col.2 through col. 4 for various oxirane carboxylic acid and the process of making them. including examples of compounds made.

Claim 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Eiter et al. US 3,246,038.

Eiter et al. teach cycloalkenyl substituted oxirane carboxylic acids, which include compounds claimed herein.. See formula III on col. 1. Particularly see col.3 through col. 4 for the process of making the compound of formula III.

Claim 59 is rejected under 35 U.S.C. 102(b) as being anticipated by Sayo et al. US 5,502,221

Sayo et al. teach cyclohexyl substituted oxirane carboxylic acids, which include compounds claimed herein.. See formula 3E on col. 2 and 3. Particularly see col.3 through col. 4 and example 2 for the process of making the compound of formula 3E .

Claims 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Leroux , Bulletin De La Societe Chimque France 344-350.

Leroux teaches several tetrahydrofuranyl and terahydropyranyl carboxylic acids which include those claimed herein. See entire document, especially page 46, table IV, experimental details and Table II for compounds made.

Claims 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagai et al. Tetrahedron Letters , 40, 4797-4801, 1966.

Nagai et al. teaches a process for making a pyran carboxylic acid which is generically claimed hereon. See page 4800 and note the scheme for conversion of XV to XVI. See the details of the process on page 4798-4799.

Claims 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Iskura Sangyo Co. JP 58032880.

The Japanese patent discloses tetrahydrofuran carboxylic acid which is generically claimed herein. See page 606 compound IV.

Claims 59-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Hiranuma et al. J. Org. Chem. 48, 5321-5326, 1983.

See page 5322, compound 10 and see page 5325 left column for the process of making.

Claims 59-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica)27, 178-184, 1992.

Wang et al. teaches compounds 8 and 9 which bear the tetrahydrofuran and tetrahydropyran carboxylic acid claimed herein. It is held that Wang et al. inherently teaches these acids for cephalotaxine alkaloids. Note In re Petering et al 133 USPQ 275; In Re Schaumann, 195 USPQ 5.

Claim 59 is rejected under 35 U.S.C. 102(e) as being anticipated by Russo-Rodriguez et al. US 6,107,291.

Russo-Rodriguez et al. teach azepine or larger medium ring carboxylic acid, which includes compounds claimed herein as intermediates for making antiinflammatory agents and other pharmaceuticals. See formula 1 on col. 3 Particularly see scheme I-III on col. 27-28,29-30 and 31-

30 for the process of making these compounds and see also example 1-30 and Table I-III for the compounds made.

Claim 59 is rejected under 35 U.S.C. 102(e) as being anticipated by Kalish et al. US 5,834,467.

Kalish et al. teach HIV protease inhibitors which include compounds claimed herein as intermediates. See formula 1 on col. 3 particularly see ring B. Note when D is a nitrogen ring B can be a monocyclic saturated 6-14 membered heterocycle as shown on col. 4 line 30-45.See col. 30 -33 for process of making the carboxylic acid and see also preparation 1-6 on col 37-45 for 1-30 for the compounds made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 59-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica)27, 178-184, 1992(Wang I) and Huang et al, the Alkaloids, Vol. XXII 157-225, 1984 in view of Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica)27, 173-177, 1992(Wang II).

Wang I teaches the tetrahydrofuran and tetrahydropyran esters of cephalotaxine as noted in the above 102 rejection. See compound 8 and 9. Note these compounds are known to exhibit antitumor activity.

Wang I differs in not making the tetrahydrofuran or pyran carboxylic acid first.

Huang et al. teaches the process for hydrolyzing the cephalotaxine alkaloids and the synthesis of the acid components. See page 165 for mild hydrolysis to get compound 7 and see route 3 on page 166. Wang II teaches a process for cyclizing the open chain acid ie compound 7 bearing a CTX group to the corresponding tetrahydrofuran compound. See page 174 of Wang II and note the last reaction shown at the bottom of the page using TsOH.

Note the starting materials are analogous in that they are compound of formula 7 with a methoxy on the tertiary carboxylic group or CTX. Thus one having ordinary skill in the art at the time of the invention was made would have been motivated to combine both the primary and secondary references and employ the process taught by these prior art to the starting materials and expect to obtain the desired product because he would have expected the analogous starting materials and reactants react similarly. It has been held that application of an old process to an analogous material to obtain a result consistent with the teachings of the art would have been obvious to one having ordinary skill. Note In re Kerkhoven 205 USPQ 1069.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wasserman et al. US 4,178,286 or Ondetti et al. US 4,154,840.

Teachings of Wasserman et al. as discussed in the above 102 rejection is incorporated herein.

As noted above, Wasserman et al. teach several azacycloalkane carboxylic acids claimed herein as intermediates same as the utility of instant invention.

Wasserman differs from the instant claims in not exemplifying with example of azacycloalkane other than azetidine. However, Wasserman et al. teaches a process for making higher ring size azacycloalkane and teaches equivalency of the exemplified 4-membered ring with those disclosed in the definition of n. See col.3 line 19-20 and lines .Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make aza cycloalkane compounds with various ring sizes as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Henning et al. US 4,849,524.

Teachings of Henning et al as discussed in the above 102 rejection is incorporated herein. As note above, Henning et al. teach process for preparing several proline derivatives claimed herein as intermediates for preparing inhibitors of angiotensin converting enzymes.

Henning differs from the instant claims in not exemplifying proline derivatives with all the R values taught therein. See col. 3 line 29-37 for few substituted prolines.

However, Henning et al. teaches both the equivalency of therein exemplified substituents with that with various R groups disclosed. See formula I on col. 2 and note the various R groups in the proline ring. Thus it would have been obvious to one having ordinary skill in the art at the time of

the invention was made to make compounds variously substituted in the proline ring as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bosies et al.US 4,409,236.

Teachings of Boises et al as discussed in the above 102 rejection is incorporated herein. As note above, Bosies et al teach several N-substituted aziridine-2-carboxylic acid derivatives which include compounds claimed herein for immuno-stimulation. See general formula shown on col. 1 line 52 and note the definition of R, R_1 and X group. Note when X= COOH, the reference teaches compounds claimed herein.

Boises et al. differs from the instant invention in not exemplifying several aziridine derivatives with all the R and R_1 values taught therein.

However, Boises et al. teaches the equivalency of therein exemplified substituents with that with various R groups disclosed. See formula I on col. 2 and note the various R and R_1 groups in the aziridine ring. Thus it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make compounds variously substituted in the aziridine ring as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

References which were properly cited in the Information Disclosure Statement have been considered but those missing , page numbers, book information etc. were not considered. Applicants should provide the missing information for consideration of those references. See attached 1449.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (703) 305-1674. The examiner can normally be reached on weekdays from 8.30 AM to 5.00 PM.

The fax phone number for the organization where this application or proceeding is assigned (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

VB

V. Balasubramanian (Bala)

8/23/2000

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